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THE APPLICATION OF STOCHASTIC APPROXIMATION METHODS TO THE BIO---ETC(U)

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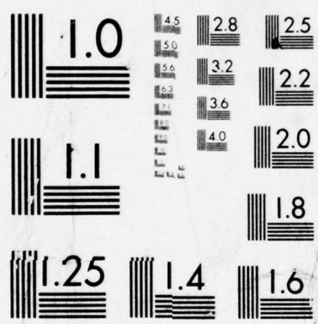

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by

10 Dan Anbar

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OFFICE OF NAVAL RESEARCH

Department of Mathematics and Statistics
CASE WESTERN RESERVE UNIVERSITY
Cleveland, Ohio

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THE APPLICATION OF STOCHASTIC APPROXIMATION METHODS TO THE BIO ASSAY PROBLEM

by

Dan Anbar
Case Western Reserve University
and
Tel Aviv University

1. Introduction. The bio assay problem of estimating the median effective dose of a preparation is probably as old as any of the important statistical problems.

With a few exceptions most of the statistical methods used are derived from fixed sample regression techniques. There are, however, many situations in which a sequential method would seem appropriate. Furthermore, the traditional bio-assay techniques rely heavily upon the assumed parametric model and the threshold model for the dose-response curve (see Sec. 2).

Stochastic approximation methods of the Robbins-Monro type seem to be attractive candidates for replacement of traditional methods when a sequential design is feasible. (e.g. there is a short time delay between application of treatment and the response).

Small sample simulations which have been carried out in the past (Wetherill (1963) and Cochran and Davis (1965)) have demonstrated a very good performance of the Robbins-Monro method versus the traditional methods.

In this paper it is shown that the Robbins-Monro procedure for estimating the Median Effective Dose (ED_{50}) is asymptotically optimal in the sense that it yields estimators with minimal asymptotic variance. Reduction of the asymptotic variance to the minimum in the usual Robbins-Monro process can be done only when the slope of the dose-response curve at the estimated value is known which implies among other things a full knowledge of the dose-response curve. This is clearly an unrealistic situation in many cases. A few authors constructed adaptive methods which achieve the minimal asymptotic variance in a purely non-parametric setting. The application of two such techniques due to Venter (1967) and Anbar (1976) is also discussed. The results of some small sample simulations are given in Section 5.

In Section 2 a more general model for the bio assay problem is developed. It is demonstrated that in general any particular assumption about the specific form of the dose-response curve is just as arbitrary as any other such assumption. In general one would not want to assume much more than that the curve possesses the properties of a distribution function and that the ED_{50} is well defined.

In Section 3 the Robbins-Monro procedure for estimating the ED_{50} is discussed and its optimality property is proved. Venter's and Anbar's adaptive versions are also discussed in Section 4. Section 5 is dedicated to some numerical studies.

2. A model for the bio-assay problem. The bio-assay problem is centered around the question of obtaining efficient techniques for estimating the median effective dose (ED_{50}) for a new preparation.

The ED_{50} is defined relative to a population of experimental animals and the following model is assumed:

(i) To every animal in the population corresponds a fixed dose x, so called "just effective dose", such that any dose smaller than x would produce no reaction when administered to the animal and any dose larger than x would produce a full reaction.

(ii) The "just effective doses" are distributed in the animal population according to the distribution $F(\frac{x-\mu}{\sigma})$ where F is a known distribution function and μ and $\sigma > 0$ are unknown location and scale parameters.

Clearly, when an animal is selected at random from the pooulation and a dose x is administered to it, the probability that it would react to this dose is $F(\frac{x-\mu}{\sigma})$. If we assume that F is symmetric around zero, then μ is the median of the "just effective doses" in the population. F is called the "dose-response curve" or the "tolerance curve" and μ is the ED_{50}.

Thus the bio-assay problem is reduced to the problem of estimating μ. The different models and techniques used, result from different choices of F which is typically selected to be either the normal or the logistic distributions.

The threshold theory which has been just described seems quite artificial. The resistance of an individual animal to a given drug depends upon a multitude of variables such as diet, environmental conditions and various physiological processes which cannot possibly be all controlled. Thus one may consider the following general model. Let U be some abstract space. Think of a point u_0 in U as a complete description of all relevant variables. Let $\rho(u,x)$ be the probability of obtaining a reaction given the conditions $u \in U$ and that dose x was administered. Assume that ρ satisfies the following two conditions:

(i) For every fixed $u \in U$, $\rho(u,x)$ is monotone non-decreasing in x.

(ii) $\lim_{x\to\infty} \rho(u,x) = 1$, $\lim_{x\to-\infty} \rho(u,x) = 0$ for every $u \in U$.

Let λ be a probability measure on U. The function

$$M(x) = \int_U \rho(u,x)\, d\lambda(u) \tag{1}$$

is the probability that a randomly selected animal would react to the dose x.

Clearly, $M(x)$ is monotone non-decreasing with $\lim_{x\to-\infty} M(x) = 0$ and $\lim_{x\to\infty} M(x) = 1$. The function M will be called the <u>tolerance curve</u>. If the equation $M(x) = 1/2$ has a unique solution at $x = \theta$, θ is the ED_{50}.

A SPECIAL CASE. Let $a(u)$, $u \in U$ be a real valued function on U. Assume that $\phi(u,x)$ depends upon u only through $a(u)$ and that

(2) $$\phi(u,x) = \psi(x - a(u)) \quad \text{where } \psi \text{ is a monotone}$$

non-decreasing function of a real variable satisfying $0 \leq \psi(t) \leq 1$ and $\psi(t) = 1 - \psi(-t)$ for all t. Furthermore assume that the distribution of $a(u)$ induced by the measure λ is given by $F(\frac{a-\mu}{\sigma})$ where F is symmetric about zero and μ and $\sigma > 0$ are location and scale parameters. In this case

$$M(\mu + x) = \int_{-\infty}^{\infty} \psi(\mu + x - a)\, dF(\frac{a-\mu}{\sigma}) = \int_{-\infty}^{\infty} \psi(x-t\sigma)dF(t)$$

$$= 1 - \int_{-\infty}^{\infty} \psi(t\sigma-x)\, dF(t) = 1 - \int_{-\infty}^{\infty} \psi(-t\sigma-x)dF(t)$$

$$= 1 - \int_{-\infty}^{\infty} \psi(\mu-x-a)dF(\frac{a-\mu}{\sigma}) = 1 - M(\mu-x) \quad .$$

M is obviously monotone non-decreasing. Furthermore, $M(\mu) = 1/2$ and if M has a positive derivative at $x = \mu$, then μ is the unique solution of the equation $M(x) = 1/2$. The threshold theory is obtained when $a(u)$ is the "just effective dose" and ψ is chosen to be the function

(3) $$\psi(t) = \begin{cases} 0 & \text{if } t < 0 \\ 1 & \text{if } t \geq 0 \end{cases} .$$

It should be noted that the tolerance curve $M(t)$ is identical with $F(\frac{t-\mu}{\sigma})$ if and only if ψ is of the simple form (3).

If f has a continuous derivative at some neighborhood of μ then one can easily check that

$$(4) \qquad M'(\mu) = -\frac{1}{\sigma^2} \int_{-\infty}^{\infty} \psi(t)\, f'(t/\sigma)dt \quad ,$$

where $M'(\mu) = \frac{d}{dt} M(t)\Big|_{t=\mu}$.

When ψ is given by (3), (4) simplifies to

$$(5) \qquad M'(\mu) = \frac{f(0)}{\sigma} \quad .$$

Remark. If one is willing to accept that the model introduced in this section is more realistic than the threshold model, then even if one knows the particular form of λ in (1) (which will be probably very rare in practice), the particular form of the dose-response curve M will still be unknown. Thus one should be very weary of using methods which depend heavily upon the mathematical form of M without studying their robustness against deviations from it.

3. Stochastic approximations. Stochastic approximations of the Robbins-Monro type are sequential procedures which are designed to estimate the zero of a regression function when the investigator can only assume some general properties of the function but not its mathematical from. The problem of estimating the ED_{50} (or any other percentile of the dose-response curve) falls under this category of problem since the ED_{50} is the solution of the equation $M(x) - 1/2 = 0$.

The Robbins-Monro procedure is the following. Let $H(x)$ be a real valued function of a real variable x. Let θ be the unique solution of the equation $H(x) = 0$. Let $\{Y_x\}$ be an observable family of random variables such that $EY_x = H(x)$ for every x. Let $\{a_n\}$ be a sequence of non-negative real numbers such that $\sum_{n=1}^{\infty} a_n = \infty$ and $\sum_{n=1}^{\infty} a_n^2 < \infty$.

Let X_1 be a random variable and define

$$X_{n+1} = X_n - a_n Y_n \qquad n = 1,2,\ldots \tag{6}$$

where Y_n is a random variable with conditional distribution given $(X_1 = x_1, \ldots, X_n = x_n)$ the same as the distribution of Y_{x_n}.

The process (6) is the Robbins-Monro process. Under some regularity conditions $X_n \to \theta$ with probability one. (See e.g. Blum (1954)). For $a_n = A_n^{-1}$, $n^{1/2}(X_n - \theta)$ converges in law to a normal random variable with mean zero and variance $\sigma^2 A^2/(2A\alpha - 1)$ where $\alpha > 0$ is the derivative of H at $x = \theta$, $\sigma^2 = \lim_{x \to \theta} E(Y_x - H(x))^2$ and A is chosen such that $2Aa > 1$. (Sacks (1958)).

The problem of efficiency of the Robbins-Monro process as measured by the asymptotic variance was studied by several authors. One can easily verify that the choice $A = \alpha^{-1}$ minimizes the asymptotic variance. When α is unknown an adaptive process can be constructed. One adaptive process was suggested by Venter (1967). Another process was studied by Anbar (1976). The two processes are optimal in the sense that their asymptotic variance is minimal. However, while Venter's procedure requires taking two observations at each approximation, in Anbar's method the observations are taken one at a time. A different way of reducing the asymptotic variance was studied by Anbar (1973) and Abdelhamid (1973). They have shown that when Y_x is distributed according to $F(y-H(x))$ where F is a known distribution, one can minimize the asymptotic variance by applying a suitable transformation to the Y_n's. When α is known, the optimal transformation yields a most efficient estimator in the sense that the asymptotic variance equals to the Cramér-Rao lower bound for estimating the zero when the regression function is linear. Fabian (1973) have constructed a process which achieves the Cramér-Rao lower bound also when α is not known.

The results of Abdelhamid, Anbar and Fabian cannot be applied to the bio-assay situation because the family of distributions of the Y_x's is not a shift family generated by a fixed distribution. However, as it is shown in this paper, in the bio-assay case the Robbins-Monro process yields a most efficient procedure when α is known and hence both Venter's and Anbar's modifications can be used to produce a most efficient sequence of estimators when α is unknown.

To apply the Robbins-Monro procedure to the bio-assay problem assume that when a dose x is applied to N subjects the investigator observes the random variable N_x - the number of subjects reacting to the dose x. If the tolerance curve is $M(x)$ then N_x is a binomial variable with parameters $(N,M(x))$. Let X_1 be the initial dose chosen by the investigator. For $n = 1,2,\ldots$ define

$$X_{n+1} = X_n - An^{-1}(P_n - 1/2) \tag{7}$$

where $P_n = N_{x_n}/N$.

The relation (7) determines sequentially a sequence of doses to be applied.

4. Asymptotically optimal procedures.

Assume that the tolerance curve $M(x)$ is monotone non-decreasing taking on values in $[0,1]$ and that $M'(x)$ exists and continuous in some neighborhood of μ and $M'(\mu) > 0$. Denote $\alpha = M'(\mu)$. It is easy to verify that in this case the conditions for convergence and asymptotic normality of the process (7) are satisfied and thus $X_n \to \mu$ with probability one and if $2\alpha A > 1$ then $\sqrt{n}(X_n - \mu)$ converges to a normal random variable with mean zero and variance $A^2/4N(2\alpha A-1)$.

Denote $P_x = N_x/N$. Let g be a function and define $M_g(x) = Eg(P_x)$. Assume that

a) $M_g(x)$ is a tolerance curve.

b) $M_g(\mu) = 1/2$.

c) $M_g(x)$ is continuously differentiable at $x = \mu$ with $M_g'(\mu) > 0$.

One can define another approximation process $X_n^{(g)}$ by replacing P_n in (7) by $g(P_n)$. If in addition one substitutes in (7) $A = [M_g'(\mu)]^{-1}$ then $X_n^{(g)} \to \mu$ with probability one and

$$\sqrt{n}\,(X_n^{(g)} - \mu) \xrightarrow{\mathcal{L}} N(0,\sigma_g^2)$$

where

(8)
$$\sigma_g^2 = \lim_{x\to\mu} E[g(P_x) - M_g(x)]^2/[M_g'(\mu)]^2$$
$$= \mathrm{Var}[g(P_\mu)]/[M_g'(\mu)]^2 \quad .$$

Now

$$M_g'(x) = \sum_{j=0}^{N} g(j/N)\binom{N}{j} \frac{d}{dx} [M^j(x)(1 - M(x))^{N-j}] \quad .$$

Simple calculations yield

(9)
$$M_g'(x) = \frac{N\,M'(x)}{M(x)[1-M(x)]} \cdot \mathrm{cov}(g(P_x),\ P_x)$$
$$= M'(x)\ \mathrm{cov}(g(P_x),P_x)/\mathrm{var}(P_x) \quad .$$

By the Cauchy-Schwartz inequality one readily obtains

(10)
$$\frac{\mathrm{Var}(g(P_x))}{(M_g'(x))^2} \geq \frac{\mathrm{Var}\ P_x}{(M'(x))^2} \qquad \text{for all } x.$$

The right hand side of (10) at $x = \mu$ is the asymptotic variance of the Robbins-Monro process (7). Since equality in (10) is achieved if and only if $g(x) = cx$ for some constant c one obtains that the Robbins-Monro procedure is indeed optimal for this problem. Note that at $x = \mu$ the right hand side of (10) equals to $[4N\alpha^2]^{-1}$ which is the Cramér-Rao lower bound for estimating μ when the tolerance curve is linear. Thus the process (7) is <u>most efficient</u> when $A = \alpha^{-1}$.

When α is unknown most efficient processes exist. They are adaptive modification of (7). Let us describe two such procedures.

<u>Venter's procedure</u>. The first approximation (dose) X_1 is arbitrary. For $n \geq 1$ the $(n+1)$st approximation is determined by the recursive relation.

$$X_{n+1} = X_n - d_n A_n^{-1} \frac{1}{2}(Y_n' + Y_n'') \tag{11}$$

where Y_n' and Y_n'' are observations at $X_n + c_n$ and $X_n - c_n$ respectively, $\{d_n\}$ and $\{c_n\}$ are sequences of positive numbers satisfying $d_n = n^{-1}(1 + O(n^{-1/2}))$ and $d_n = cn^{-\gamma}$ $(c > 0\ ,\ 0 < \gamma < 1/2)$ and A_n is an estimator for α determined as follows.

Denote the truncation of a function f in the interval $[a,b]$ by $[f]_a^b$. That is

$$\begin{aligned} [f(x)]_a^b &= b \quad \text{if} \quad f(x) \geq b \\ &= f(x) \quad \text{if} \quad a < f(x) < b \\ &= a \quad \text{if} \quad f(x) \leq a \ . \end{aligned}$$

Let

$$B_n = n^{-1} \sum_{j=1}^{n} (Y_j' - Y_j'')/2c_j \quad , \quad n = 1,2,\ldots \ .$$

Then $A_n = [B_n]_a^b$ where a and b are two known numbers satisfying $a < \alpha < b$. Venter has shown the following.

1. $X_n \to \mu$ a.s. as $n \to \infty$.
2. For $1/4 < \gamma < 1/2$, $n^{1/2}(X_n - \mu)$ converges in distribution to a normal random variable with mean zero and variance $\sigma^2/2\alpha^2$. For $\gamma = 1/4$ the asymptotic distribution of $n^{1/2}(X_n - \mu)$ is normal with mean $-2\alpha_2 c^2/\alpha$ and variance $\sigma^2/2\alpha^2$, where α_2 is the second derivative of M at $x = \mu$.

Venter also investigated the rate of convergence of A_n to α. As it turns out the rate of convergence of A_n depends upon the choice of γ and c. The smaller γ is and the larger c is the better is the rate of convergences. However, when $\gamma \leq 1/4$ a bias is introduced in the estimation of μ which increases with c. Thus Venter recommended to use $\gamma = 1/4$ and a moderate value of c. In the next section the performance of Venter's procedure is examined for various values of c via computer simulations.

Anbar's procedure. The first approximation X_1 is chosen arbitrarily. For $n \geq 1$ the $(n+1)$st approximation is determined by the recursive relation

$$X_{n+1} = X_n - A_{n-1}^{-1} n^{-1} Y_n \tag{12}$$

where Y_n is an observation at X_n and $A_n = [B_n]_a^b$ where B_n is given by

$$B_n = \frac{\sum_{i=1}^{n} (X_i - \bar{X}_n) Y_n}{\sum_{i=1}^{n} (X_i - \bar{X}_n)^2}$$

for $n \geq 2$ and B_0 and B_1 are arbitrary positive numbers. The numbers a and b are assumed to be known and $a < \alpha < b$. Anbar (1976) has shown that $A_n \to \alpha$ a.s. and $n^{1/2}(X_n - \mu)$ converges in distribution to a normal random variable with mean zero and variance σ^2/α^2.

Both Venter and Anbar have suggested to compute B_n by summing for some integer $m = m(n)$ to n instead of from 1 to n in order to disregard large deviations which may occur in the first approximation.

5. Numerical results. In this section some numerical studies are summarized. For reference purposes the numerical simulations were carried out along the same lines as the studies of Cochran and Davis (1965). The dose-response curve was chosen to be the standard normal cumulative curve. Venter's and Anbar's procedures were simulated for different total number of experiments available $(n = 12, 24)$ and different number of experiments performed at each stage $(m = 1,2,3)$. The mean square error and the bias were estimated on the basis of 100 independent repetitions of each simulation. We have followed Venter's suggestion and chose $\gamma = 1/4$. Tables 1 through 6 give the MSE and bias for both Anbar's and Venter's methods as functions of the starting point x_0 for the different values of n and m. Venter's method was simulated for different values of c. The slope at $x = \mu$ is $\alpha = (2\pi)^{-1/2} = .3989$. The truncation points for the estimating the slope in both methods were chosen to be $a = .5\alpha = .1995$ and $b = 1.5\alpha = .5984$.

An examination of the simulations results reveals some interesting phenomenae. The most striking phenomenon is the higher dependability of Venter's method on the value of the initial dose X_0. Both MSE and bias tend to increase fairly rapidly with X_0. This is generally true for all values of c. However, the sensitivity of Venter's Method to error in the initial dose increases significantly with c. On the other hand if the initial dose is close to the ED_{50} a high value of c produces very small MSE and bias. As compared to Venter's method Anbar's method tends to produce MSE's comparable to or higher than Venter's when the error in the initial dose is small. For large error in the initial dose Anbar's method yields MSE's and biases significantly smaller than Venter's method. It seems that Anbar's method is fairly insensitive to errors in the initial dose. Comparing with Cochran and Davis results, the MSE involved in using Anbar's method are very similar to those obtained by using the optimal Robbins-Monro procedure when the slope of the dose-response curve at the ED_{50} is known. Another important observation is that the bias component in the MSE is typically much larger in Venter's method than in Anbar's. This is to expected for large values of n since for $\gamma = 1/4$ Venter's procedure is asymptotically biased. It seems that this fact shows up also for very small values of n. The values of the slope estimates are not reported here. They were computed in the study. Venter's procedure almost invariably over estimated the slope. In fact almost all values were very close to the upper truncating point. On the other hand, Anbar's method produced reasonable estimates.

To summarize, if one has a very good apriory knowledge about the location of the ED_{50}, Venter's method will produce very efficient estimators. If on the other hand one does not have a very reliable prior knowledge, the use of Anbar's method involves a very little risk.

Table 1. MSE and BIAS for Anbar's and Venter's procedures. $n = 12$, $m = 1$.

	ANBAR		VENTER									
			C = .5		C = 1.3		C = 1.7		C = 2.1		C = 2.9	
X_0	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS
0.0	.1504	.0121	.1219	-.0370	.0735	-.0348	.0537	.0400	.0517	-.0097	.0071	-.0173
.2	.1779	-.0461	.0982	-.0267	.0802	.0677	.0606	.1226	.0469	.1367	.0394	.1826
.4	.1419	.0361	.1499	.1487	.0898	.1325	.1093	.2194	.0953	.2333	.1446	.3678
.6	.1654	.0449	.1453	.0859	.1414	.2394	.1740	.3101	.2370	.4179	.3239	.5548
.8	.1543	.0280	.1155	.1343	.1630	.2888	.2370	.3643	.3668	.5361	.5043	.6899
1.0	.1750	.0257	.1009	.1555	.2296	.3455	.3365	.4741	.5058	.6360	.7578	.8410
1.2	.1070	.0921	.1632	.2789	.2754	.4138	.4015	.5468	.6396	.7330	.9769	.9529
1.4	.1410	.0765	.1700	.3027	.3444	.4627	.6185	.7032	.6826	.7657	1.1663	1.0451
1.6	.1762	.1408	.1930	.3530	.3427	.4927	.7437	.7678	.9278	.9072	1.5256	1.2001
1.8	.1734	.2334	.2138	.3858	.5704	.6591	.8461	.8436	1.0805	.9751	1.7320	1.2753
2.0	.1243	.1208	.3440	.5312	.6464	.7224	.9513	.8854	1.2661	1.0608	2.0851	1.4085
2.2	.1707	.2925	.4134	.5851	.7623	.8182	1.0887	.9885	1.4917	1.1539	2.5991	1.5735
2.4	.2471	.4424	.5555	.7143	.8602	.8719	1.1293	1.0141	1.7961	1.2801	2.7121	1.6121
2.6	.1410	-.0615	.6608	.7873	1.0851	.9860	1.4258	1.1402	1.8301	1.3100	3.0464	1.7106
2.8	.1667	-.0486	.9723	.9584	1.2932	1.1009	1.5687	1.2069	2.0031	1.3756	3.1893	1.7378
3.0	.5115	.6380	1.1981	1.0745	1.5585	1.2107	1.8530	1.3196	2.3536	1.4976	3.6268	1.8767
3.2	.1471	.1981	1.5571	1.2333	1.8812	1.3575	2.1288	1.4396	2.6555	1.5931	3.8143	1.9151
3.4	.9665	.9687	1.9799	1.3737	2.3096	1.5059	2.6065	1.5920	2.9874	1.6994	4.2141	2.0177
3.6	.2085	-.0030	2.5704	1.5910	2.9112	1.6844	3.1166	1.7441	3.3391	1.8027	4.5416	2.0972
3.8	.1684	-.0110	2.9882	1.7058	3.3624	1.8077	3.6561	1.8851	3.7988	1.9345	5.1210	2.2354

TABLE 2. MSE and BIAS for Anbar's and Venter's procedures. n = 12, m = 2.

	ANBAR		VENTER									
			C = .5		C = 1.3		C = 1.7		C = 2.1		C = 2.9	
X_0	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS
0.0	.0005	-.0031	.1217	-.3488	.0000	.0000	.0000	.0000	.0000	.0000	.0000	.0000
.2	.4006	-.6321	.0826	-.2875	.0400	.2000	.0400	.2000	.0400	.2000	.0400	.2000
.4	.3600	-.6000	.1336	-.3654	.0676	.2599	.1600	.4000	.1600	.4000	.1600	.4000
.6	.0575	-.2387	.0929	-.3047	.0632	.2513	.3600	.6000	.3600	.6000	.3600	.6000
.8	.0256	-.1600	.1457	-.3804	.0605	.2361	.3467	.5879	.6400	.8000	.6400	.8000
1.0	.0000	-.0003	.0373	-.1880	.0549	.2293	.4226	.6498	.7367	.8580	1.0000	1.0000
1.2	.0582	-.2410	.0021	.0120	.1867	.4293	.3256	.5672	.7203	.8482	1.4000	1.2000
1.4	.0820	-.2824	.0021	.0013	.0492	.2104	.3979	.6289	1.0996	1.0482	1.9600	1.4000
1.6	.1070	-.3218	.0435	.2027	.1797	.4029	.6895	.8289	.6916	.8302	2.1223	1.4565
1.8	.1337	-.3643	.0721	.2629	.3808	.6029	.3792	.6014	1.0589	1.0278	2.1003	1.4490
2.0	.0534	-.2132	.0761	.2561	.3659	.5944	.6598	.8014	1.5100	1.2278	2.7102	1.6458
2.2	.0911	-.2997	.4432	.6586	.6437	.7944	1.0204	1.0014	1.0165	.9992	3.3923	1.8402
2.4	.0143	-.1108	.5546	.7370	.2748	.5204	.9931	.9894	1.4562	1.1992	2.6427	1.6246
2.6	.1052	-.3244	1.1311	1.0544	.5230	.7204	.7592	.8678	1.9759	1.3992	3.3325	1.8246
2.8	.0155	-.1244	1.3051	1.1330	.8512	.9204	.7870	.8851	1.9286	1.3823	4.0813	2.0175
3.0	.3022	-.5497	.4132	.6347	.6398	.7944	.6479	.8043	1.1285	1.0606	3.2430	1.7954
3.2	.3105	-.5564	.7071	.8347	.9976	.9944	.2726	.5215	1.0726	1.0350	3.9845	1.9899
3.4	.1279	-.3564	3.0922	1.7457	1.4354	1.1944	.6109	.7799	.7889	.8882	3.9190	1.9744
3.6	.0259	-.1606	1.5372	1.2271	.4699	.6826	.9629	.9799	1.1731	1.0822	3.0542	1.7462
3.8	.0281	-.1674	2.0680	1.4271	.9684	.9775	1.3830	1.1716	1.7510	1.3215	2.7787	1.6663

Table 3. MSE and BIAS for Anbar's and Venter's procedures. $n = 12$, $m = 3$.

	ANBAR		VENTER							
			C = .5		C = 1.3		C = 1.7		C = 2.1	
X_0	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS
0.0	.1130	.0377	.0744	-.0283	.0382	-.0104	.0274	-.0081	.0134	-.0097
.2	.1181	.0671	.0726	.0513	.0586	.1360	.0479	.1485	.0551	.1992
.4	.1050	.0482	.0741	.1591	.0931	.2524	.1252	.3151	.1367	.3513
.6	.0930	.0966	.1070	.1739	.1610	.3302	.2246	.4314	.2735	.4984
.8	.1010	.1078	.1188	.2486	.2903	.4662	.4041	.6106	.4597	.6475
1.0	.1675	-.0345	.1649	.3113	.3470	.5408	.5525	.7088	.6939	.8134
1.2	.1094	.1433	.2124	.4059	.4953	.6655	.6755	.7801	.9507	.9518
1.4	.1157	.1593	.3221	.5306	.6167	.7501	.9286	.9342	1.1650	1.0564
1.6	.0961	.1112	.4478	.6428	.8468	.8851	1.1228	1.0260	1.4188	1.1656
1.8	.1340	.1999	.6303	.7561	.9981	.9532	1.3916	1.1551	1.8041	1.3273
1.9	.0930	.0457	.6853	.7915	1.1861	1.0538	1.5150	1.2117	2.0133	1.3971

Table 4. MSE and BIAS for Anbar's and Venter's procedures. $n = 24$, $m = 1$.

	ANBAR		VENTER							
			C = .5		C = 1.3		C = 1.7		C = 2.1	
X_0	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS
0.0	.0764	-.0127	.0778	-.0196	.0499	.0140	.0351	.0230	.0289	-.0096
.2	.0803	-.0164	.0652	-.0113	.0588	.0652	.0594	.1173	.0571	.1402
.4	.0769	.0116	.0688	-.0022	.0806	.0902	.0508	.1289	.0852	.1906
.6	.0721	-.0307	.0652	.0482	.0877	.1610	.1031	.2190	.1402	.2471
.8	.0832	.0401	.0878	.1190	.1474	.2405	.1806	.3257	.1988	.3742
1.0	.0782	-.0387	.0666	.1184	.1390	.2488	.2021	.3526	.3488	.5281
1.2	.0770	.0296	.0784	.1569	.1508	.2836	.2497	.4239	.3934	.5560
1.4	.0749	.0055	.0921	.1674	.1907	.3296	.3162	.4627	.4741	.6267
1.6	.0891	.1429	.1082	.2495	.2818	.4384	.4555	.5999	.6152	.7230
1.8	.0709	-.0292	.0950	.2398	.3188	.4907	.4731	.6187	.7859	.8122
2.0	.1049	.0872	.1718	.3427	.3317	.4991	.5300	.6604	.8615	.8727

Table 5. MSE and BIAS for Anbar's and Venter's procedures. $n = 24$, $m = 2$.

	ANBAR		VENTER							
			C = .5		C = 1.3		C = 1.7		C = 2.1	
X_0	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS
0.0	.0003	-.0022	.1070	-.3272	.0017	-.0057	.0000	.0000	.0000	.0000
.2	.0046	-.0621	.0951	-.3083	.0169	.1302	.0400	.2000	.0400	.2000
.4	.0063	-.0560	.0761	-.2758	.0242	.1555	.1600	.4000	.1600	.4000
.6	.0016	-.0372	.1063	-.3260	.0097	.0987	.1697	.4119	.3600	.6000
.8	.0057	-.0728	.0858	-.2930	.0272	.1534	.1616	.4018	.4179	.6464
1.0	.0145	-.0900	.0913	-.3022	.0231	.1466	.1550	.3937	.4520	.6723
1.2	.0124	-.1096	.0583	-.2415	.0309	.1743	.1579	.3949	.4395	.6629
1.4	.0184	-.1284	.0633	-.2513	.0198	.1268	.1406	.3743	.6271	.7916
1.6	.0451	-.1883	.0035	-.0527	.0300	.1503	.3303	.5743	.4324	.6568
1.8	.0290	-.1656	.0011	.0076	.1325	.3482	.1324	.3481	.5995	.7739
2.0	.0213	-.1437	.0119	.0998	.1239	.3415	.3116	.5481	.9460	.9717
2.2	.0428	-.2028	.0502	.2173	.3005	.5415	.5709	.7481	.5700	.7475
2.4	.0347	-.1805	.0812	.2784	.3695	.6036	.5567	.7412	.9090	.9475
2.6	.0398	-.1977	.2920	.5334	.4940	.7002	.6501	.8031	1.3280	1.1475
2.8	.0188	-.1290	.4650	.6745	.4120	.6395	.8121	.8991	1.3079	1.1404

Table 6. MSE and BIAS for Anbar's and Venter's procedures. $n = 24$, $m = 3$.

	ANBAR		VENTER							
			C = .5		C = 1.3		C = 1.7		C = 2.1	
X_0	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS	MSE	BIAS
0.0	.0650	-.0166	.0429	.0303	.0354	-.0310	.0233	-.0118	.0197	.0028
.2	.0613	-.0102	.0517	.0634	.0351	.0564	.0363	.1087	.0303	.1274
.4	.0599	.0693	.0564	.0889	.0805	.1821	.0850	.2424	.1070	.3042
.6	.0649	.0696	.0534	.1014	.1150	.2560	.1605	.3519	.2092	.4353
.8	.0569	.0965	.0697	.1816	.1791	.3630	.2185	.4256	.3499	.5569
1.0	.0742	.1234	.0746	.2021	.2410	.4521	.3830	.5862	.5286	.7047
1.2	.0662	.1566	.1178	.2844	.3298	.5408	.5053	.6705	.7487	.8479
1.4	.0743	.0843	.1641	.3577	.4091	.6101	.6390	.7638	.9129	.9345
1.6	.0638	.0941	.2321	.4438	.5055	.6827	.8152	.8771	1.1129	1.0373
1.8	.1071	.1779	.3277	.5429	.6188	.7577	.9794	.9636	1.2995	1.1194

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A new general model for the bio-assay problem is introduced. It is shown that when the slope of the dose-response curve and the median effective dose is known, the Robbins-Monro method yields an asymptotically optimal estimation procedure. Adaptive procedures are discussed for the case of unknown slope. Results of Monte Carlo studies are given.

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